REMARKS

Claims 37-48 remain pending. Favorable reconsideration is respectfully requested.

The present invention relates to a process of lyophilization for the preparation of a piroxicam:β-cyclodextrin inclusion compound in a 1:2.5 molar ratio conducted on a kilogram scale, comprising:

(a) dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and ammonium hydroxide in water brought to a temperature of at least 60 °C;

(b) pouring the piroxicam and β-cyclodextrin dissolved in water from (a) on temperature-controlled shelves of a freeze-dryer pre-cooled to a temperature of at least -30 °C to lower the temperature of the solution to -10 °C at a cooling rate equal to or higher than 1 °C/min, to produce a frozen solution;

(c) further lowering the temperature of the frozen solution to at least -20 °C; and

(d) drying the frozen solution under vacuum,

where the inclusion reaction is complete with complete amorphization of the inclusion compound and complete conversion of the piroxicam to the zwitter-ionic form.

See Claim 37.

The rejection of the claims under 35 U.S.C. §103(a) over Chiesi et al. is respectfully traversed. The reference fails to suggest the claimed process.

Regarding the Rule 132 Declaration of record, the Examiner states in the Final Rejection that:

> The declaration fails to set forth any convincing reason or evidence that indicates their claimed process produces a product that is not the same or that is different from the product of the applied prior art document...". [Office Action at page 5 and page 8.]

Although the lyophilized product disclosed in Chiesi et al. is completely amorphous and does not exhibit the typical exothermic peak of free piroxicam at about 200°C, these

features are ***not*** sufficient to argue that it should *ipso facto* correspond to the product obtained from the claimed process. As demonstrated by the article Rendeti et al. (*Int. Journal of Pharmaceutics*, 129 (1996), 289-294); copy submitted herewith), a mixture of the two amorphous components and a "true" inclusion compound cannot be differentiated on the basis of the absence of the endothermal peak of free piroxicam, as this is a feature shared by both entities-- i.e., amorphous mixture and inclusion compound.

For a "true" inclusion compound to be formed, it is necessary that piroxicam assume a zwitter-ionic structure with positive and negative charges.

The Examiner's arguments and reasoning are based on hindsight. The Examiner's position is that a person of ordinary skill, passing from lab scale to an industrial scale, would have applied a high cooling rate of "freeze" the solution and hence maintain in the solid state the same structure of the inclusion complex in solution, with piroxicam in the zwitter-ionic form.

In the claimed method, the shelves of the freeze-drier are pre-cooled to a temperature of at least -30°C in such a way as the temperature of -10°C is reached at a rate equal to or higher than 1°C/min. The claimed method does not specify simply cooling the solution to a temperature of -10°C then further to -20°C, as stated by the Examiner on page 4, lines 1-4.

This difference is very important.

To support the non-obviousness of such a step, Applicants draw the attention of the Examiner to the data reported in the Rule 132 Declaration, filed on August 16, 2007, which demonstrates that the operating according to the teaching of the art, during the cooling, at a temperature of 50-55°C, β-cyclodextrin begins to recrystalllize causing de-complexation of piroxicam.

In the lack of any further evidence, a person of ordinary skill would have come to the conclusion that the problem was related to a decrease in the aqueous solubility of β-cyclodextrin due to its increased amount of hence would have simply adjusted the volume of water-- i.e., such a person would have increased the volume and diluted the solution.

In this respect, the applicant respectfully confirms that, contrary to the Examiner's position, what happens during the cooling, at 50-55°C, is relevant since, if β-cyclodextrin begins to recrystallize, it is no longer available for forming an amorphous "true" inclusion compound. In other words, if this happens, the obtained product would be an amorphous complex with a molar ratio different from 1:2.5 plus some crystalline β-cyclodextrin.

In view of the foregoing, the claimed process is not suggested by Chiesi et al. Accordingly, the subject matter of the pending claims is not obvious over this reference. Withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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